

POSTER PRESENTATION

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Associations of Fc gamma receptor (FcγR2a, FcγR3a and FcγR2c) genotype with outcome in metastatic renal cell carcinoma (mRCC) patients receiving high dose interleukin 2 (HD-IL2)

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HD-IL2 was given to patients with mRCC in a prospective trial (ClinicalTrials.gov ID: NCT00554515) that demonstrated an overall response rate of 25%. To identify predictors of response, we genotyped patients for single nucleotide polymorphisms (SNPs) in FcγR genes: FcγR2a, FcγR3a, and FcγR2c. These FcγRs are variably expressed on immune cells, and bind to the IgG portion of antibodies, triggering activation.

FcγR2a [SNP = histidine/arginine (H/R); expressed on neutrophils, monocytes-macrophages and antigen-presenting cells (APCs)] and FcγR3a [SNP = valine/phenylalanine (V/F); expressed on NK cells and some APCs] impact patient response to immunotherapy [mainly monoclonal antibody-based (mAb) therapies] in several malignancies, as both FcγR2a-H and FcγR3a-V have higher antibody binding affinity than FcγR2a-R or FcγR3a-F, respectively. FcγR2c, also expressed on NK cells, has a SNP that regulates its expression [C nucleotide = expression; T nucleotide = non-expression (C/T)]. About 20-40% of individuals express FcγR2c; little is known about the role of FcγR2c expression in cytokine-based immunotherapy.

We found associations of FcγR genotypes with patient response to HD-IL2. Dual combination analyses of FcγR3a with FcγR2a genotypes revealed significantly improved %Tumor Shrinkage in patients with either FcγR3a-VV and/or FcγR2a-HH (n=34) as compared to

those patients genotyped as FcγR3a-VF or FF with FcγR2a-HR or RR (n=70) (p=0.047). For analyses including both FcγR3a and FcγR2c genotypes, significantly improved OS was seen in those with ≥2 alleles of either FcγR3a-V and/or FcγR2c-C (n=27) vs. those with < 2 alleles of either FcγR3a-V and/or FcγR2c-C (n=79) (p=0.013). We further considered combinations that included the genotypes of all 3 genes; we identified 42 patients with “favorable” genotypes and 64 with “unfavorable”. We saw significant improvement in the % Tumor shrinkage (p = 0.033) and a trend for improvement in OS (p = 0.071) in the “favorable genotype” group.

As reported previously by others, some cancer patients make endogenous anti-tumor Ab. The association of these “favorable” FcγR genotypes with outcome suggests there may be a beneficial interaction of “favorable” FcR genotypes with endogenous anti-tumor Ab. Favorable FcγRs may support the induction of *in vivo* antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP). In addition, ADCP by APC with a favorable pattern of FcγRs, may be playing a role in enhancing induction of effective adaptive immunity, via augmented antigen presentation. Further analyses are needed to validate these exploratory findings and clarify the mechanisms by which these favorable FcγR genotypes are associated with improved outcome in these patients with mRCC treated with HD-IL2.

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